IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNIVERSITY OF MASSACHUSETTS and CARMEL LABORATORIES, LLC, Plaintiffs, v. L'ORÉAL USA, INC., Defendant.	C.A. No. 17-cv-868-CFC-SRF

PLAINTIFFS' RESPONSIVE CONCISE STATEMENT OF FACTS IN FURTHER SUPPORT OF PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT OF NON-OBVIOUSNESS

DATED: October 16, 2020

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Plaintiffs' Responses to Defendant's Allegedly Undisputed Facts[1]		
	Allegedly Undisputed Facts	**Plaintiffs' Response**
11	Dr. Kasting's obviousness opinions address: (1) the scope and content of the prior art (Ex. C, ¶¶ 43-75; Ex. E, ¶ 7-38); (2) the disclosures of the prior art as compared to the elements of the patents-in-suit (Ex. C, ¶¶ 188-217, 224-40; *see also id.* at ¶¶ 77-187); (3) motivation to combine and reasonable expectation of success (Ex. C, ¶¶ 218-23; Ex. E, ¶ 86-96); (4) the level of skill in the art (Ex. C, ¶ 31); and (5) secondary considerations (Ex. C, ¶ 242; Ex. E, ¶¶ 86-96). His opinions further include an identification of the references that alone and/or in combination render the patents-in-suit obvious (Ex. C, ¶¶ 223, 241).	Undisputed to the extent Kasting's reports contain the cited paragraphs. L'Oréal's characterization of those paragraphs is disputed. D.I. 263, at 1-3.
12	The prior art: (1) taught that topically-applied adenosine was effective at improving the condition of the skin; (2) disclosed the use of formulations and ingredients suitable for delivery of adenosine to the dermis; and (3) taught known benefits of delivering active agents such as adenosine to the dermis. (Ex. C, ¶¶ 218-23.)	Disputed. *See, e.g.*, AppxG000002-15.[2]

[1] The Court's rule appears to be that concise statements of fact may only be 1750 words total, but L'Oréal's three opposition statements of fact total 3750 words (fewer than 1750 each). In order to respond, Plaintiffs have had to exceed a total of 1750 words, but have made every effort to keep their responses as concise as possible.

[2] Citations to "Ex. __" are to L'Oréal's exhibits. Citations to "AppxG__" are to Plaintiffs' reply appendix.

13	A person of ordinary skill in the art knew that, "when topically applied, only a portion of the drug will reach 'the dermal cells.'" (Ex. C, ¶ 216.)	To the extent L'Oréal means a "topically applied composition," undisputed that "100% of [an] applied dose" is "never achieved." Ex. 12, ¶ 37. L'Oréal's inference that some "portion" of the drug will necessarily reach the dermal cells is disputed. *Id.*; *see also* App'xD000024-28.
14	The prior art specifically correlated 0.1% concentrations of adenosine-related compounds in the composition with 10-4 M to 10-6 M at the dermis. (Ex. C, ¶¶ 216, 220.)	Disputed. The cited paragraphs discuss the '089 and JP915 references. Ex. C, ¶¶ 216, 220. The '089 patent discloses the use of kinetin, not adenosine, and specifically contrasts the use of kinetin on fibroblast cells with the use of "adenosine analogs" and warns against adenosine analogs as likely to lead to cell death. AppxG000007; Ex. I, ¶ 146. JP915, which Plaintiffs dispute is prior art, teaches away from using any compound other than the "specific cAMP derivative" disclosed, explaining that they have substantial "drawbacks" and directing skilled artisans to use only the disclosed "specific" compounds. AppxG000010.

15	Named inventor Dr. Dobson agreed that, "[i]f someone was trying to develop a formulation containing adenosine and -- that could be used to enhance the condition of the skin, that would be -- they would have a reasonable expectation that they could succeed in doing so in the 1997 time period." (Ex. O at 147:18-24; Ex. C, ¶ 220.)	Undisputed that when asked "[i]f someone was trying to develop a formulation containing adenosine and -- that could be used to enhance the condition of the skin, that would be -- they would have a reasonable expectation that they could succeed in doing so in the 1997 time period; correct?" Dobson answered "Yes." Ex. O, at 147:18-24. L'Oréal's inferences are disputed.
16	Dr. Dobson further testified that, in 1997 adenosine could be added to "well-known" "base formulation[s]" that, when topically applied, resulted in "a decrease in elasticity and a diminution of fine lines and wrinkles," which he understood to mean that "adenosine in the concentrations that are claimed in the patent[s-in-suit] had reached the dermal layer." (Ex. O at 136:25-137:25.)	Undisputed that Dobson testified he prepared adenosine compositions, applied them to himself, and observed resulting skin enhancement. Ex. O, at 134:14-23. Undisputed that when asked, "Based on that assessment, you understood that adenosine in the concentrations that are claimed in the patent had reached the dermal layer?" Dobson responded, "Yes, I did assume that." *Id.*, at 137:20-25. L'Oréal's inferences are disputed.
17	Plaintiffs' expert Dr. Bozena Michniak-Kohn opined that "a skilled artisan would have been able to use the teachings of, for example, Singh, to achieve the requisite penetration of adenosine to the dermal cells." (Ex. I, ¶¶ 150, 220, 228-29.)	Disputed. Michniak-Kohn opined "[W]hile a skilled artisan would have been able to use the teachings of, for example, Singh to achieve the requisite penetration of adenosine to the dermal cells—in contrast to Dr. Kasting's enablement argument—in light of the prior art, a skilled artisan would not have known the benefits of such action, and would not have been motivated to achieve those results." Ex. I, ¶ 150.

18	Dr. Michniak-Kohn testified that it would "be possible to make a formulation containing adenosine using commonly known excipients in the 1997-1998 time period to deliver adenosine to the dermis in the claimed concentration ranges." (Ex. U at 85:19-24.)	Undisputed.
19	Dr. Michniak-Kohn testified that it would be "possible to formulate a composition containing adenosine using commonly known techniques that would deliver adenosine to the dermis in the claimed concentration ranges." (Ex. U at 86:6-11.)	Undisputed.
20	Dr. Majella Lane conducted *in vitro* testing of the composition of Example 5 from the prior art DE107 and an example from the prior art JP153 and found that both compositions resulted in the claimed concentrations of adenosine being achieved at the dermis. (Ex. F, ¶¶ 16, 18-20, 34; Ex. C, ¶ 214.)	Undisputed that Lane's report says she conducted testing of two formulations and opined that "if Plaintiffs contend that such Franz diffusion cell testing is an appropriate methodology for determining [transdermal permeation] the experiments . . . show that applying topically the DE107 and JP153 formulations causes adenosine to penetrate through the epidermal layer to apply to the dermal cell layer in those claimed numerical concentration ranges." Ex. F, ¶ 36. L'Oréal's inferences are disputed.

21	A person of ordinary skill in the art would have been able to account for the factors affecting skin permeation in designing a topical composition for delivery of adenosine to the dermis. (Ex. C, ¶¶ 218-23; Ex. I, ¶¶ 228-29 ("a skilled artisan would have been able to formulate and test a composition using commonly available and well understood methods in 1997 to determine the concentration of adenosine that is applied to the dermal cells."), *id.* at ¶ 150.)	Undisputed that Michniak-Kohn opined that, if presented with the patents-in-suit, ("a skilled artisan would have been able to formulate and test a composition using commonly available and well understood methods in 1997 to determine the concentration of adenosine that is applied to the dermal cells." L'Oréal's inferences are disputed.
22	The prior art teaches that 0.1% adenosine compositions are safe and effective to improve skin condition. (*See*, *e.g.*, Ex. C, ¶¶ 215-16, 220, 223.)	Undisputed.
23	The prior art teaches that 0.1% adenosine analog (*e.g.*, kinetin, c-AMP derivatives) compositions are effective to improve skin condition. (Ex. C, ¶¶ 215-16, 220, 223.)	Undisputed.
24	The prior art concerning adenosine analogs (*e.g.*, kinetin, c-AMP derivatives) taught designing a topical composition containing 0.1% of the adenosine analog to deliver approximately 10-4 M to 10-6 M of that compound to the dermis. (Ex. C, ¶¶ 215-16, 220, 223.)	Disputed. The '089 patent discloses the use of kinetin, not adenosine, and specifically contrasts the use of kinetin on fibroblast cells with the use of "adenosine analogs" and warns against adenosine analogs as likely to lead to cell death. AppxG000007; Ex. I, ¶ 146.
25	Dr. Michniak-Kohn agreed that prior art U.S. Patent No. 5,731,089 discloses compositions containing 0.1% kinetin "that could be used to achieve" concentrations of 10-4 M to 10-6 M at the dermal fibroblasts. (Ex. U at 285:23-286:20; Ex. FF, 13:19-23, 235-22.)	Undisputed that Michniak-Kohn testified that the '089 patent discloses that "when kinetin is used the preferred concentration range is about 10^{-6} and $5x10^{-4}$ molar in tissue culture medium." Ex. U, at 285:19-22.

26	Adenosine and adenosine-related compounds, including kinetin and cyclic-AMP derivatives, are chemically and structurally similar. (Ex. C, ¶¶ 218-19, 198 n.18, 209 n.20; Ex. E, ¶¶ 78-81.)	Disputed. The alleged prior art references specifically distinguish between kinetin, cAMP derivatives, and other adenosine analogs. AppxG000007, 10; Ex. I, ¶ 146.
27	The prior art discloses adenosine and adenosine related compounds in the same references and teaches that they can be used interchangeably in comparable concentrations and formulations for the same purposes. (Ex. C, ¶¶ 218-19, 198 n.18, 209 n.20; Ex. E, ¶¶ 78-81.)	Disputed. The alleged prior art references specifically distinguish between kinetin, cAMP derivatives, and other adenosine analogs. AppxG000007, 10; Ex. I, ¶ 146.
28	Dr. Michniak-Kohn testified that a scientist would have been able to make conclusions about the biological and physical properties of adenosine, including how adenosine would work in the human body, based on references that discuss adenosine analogs and adenosine derivatives. (Ex. U at 218:3-219:23.)	Disputed. Michniak-Kohn testified that references about adenosine derivatives "would have taught the POSA about the state of the art at the time," that references discussing adenosine analogues and adenosine derivatives "would have taught the POSA various facts" about "adenosine-like compounds," and that a POSA would look to "anything that referred to adenosine itself" to learn about adenosine. Ex. U, at 218:30-219:23.

DATED: October 16, 2020

Respectfully submitted,

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APPENDIX IN SUPPORT

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNIVERSITY OF MASSACHUSETTS and CARMEL LABORATORIES, LLC, Plaintiffs, v. L'ORÉAL USA, INC., Defendant.	C.A. No. 17-cv-868-CFC-SRF

DECLARATION OF BEATRICE FRANKLIN

I, Beatrice Franklin, declare as follows:

I am an attorney at the law firm Susman Godfrey, L.L.P. and am counsel of record for Plaintiffs University of Massachusetts and Carmel Laboratories, LLC ("Plaintiffs") in the above-captioned matter. I hereby submit this declaration in support of Plaintiffs' Motion for Partial Summary Judgment of Non-Obviousness.

1. Attached as Exhibit 1 is a true and correct copy of excerpts from the July 21, 2020 expert report of Dr. Bozena Michniak-Kohn.

Dated: October 16, 2020

/s/ Beatrice Franklin
Beatrice Franklin

EXHIBIT 1

RESTRICTED—ATTORNEYS EYES ONLY

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNIVERSITY OF MASSACHUSETTS and CARMEL LABORATORIES, LLC, Plaintiffs, v. L'ORÉAL USA, INC., Defendant.	Case No. 1:17-cv-00868-CFC-SRF

REBUTTAL EXPERT REPORT OF BOZENA MICHNIAK-KOHN, PH.D.
REGARDING VALIDITY

Bozena Michniak-Kohn, Ph.D.

July 21, 2020
DATE

the filing date of the inventor's patent application. The diligence need not be continuously reasonable, but rather reasonably continuous.

II. ALLEGED PRIOR ART CITED IN THE KASTING AND LANE REPORTS

31. In this section, I respond briefly to the characterizations of the purported prior art identified by Kasting and Lane in their reports.

A. Adenosine

32. Adenosine is a naturally occurring compound; it is not itself an invention or publication and is not prior art. In the *Physician Desk Reference* cited by Dr. Kasting, adenosine is indicated for "Rapid Bolus Intravenous Use" as a heart treatment,[1] not topical use as a skin treatment.

B. DE590

33. DE590 (German Patent Application 1 617 590) discloses "cosmetic agents suitable for care of the skin, the scalp, the hair, the nails and the teeth and characterized by the content of an adenyl derivative." DE590 at 1. DE590 teaches such "adenyl derivatives," which may include "[a]denosine and the nucleotides derived therefrom," may be used on "the skin, the scalp and the remaining surface of the body," by "incorporat[ing]" them in "a cream, a lotion, a hair tonic, a shampoo or any arbitrary other cosmetic formulation." *Id.* at 2, 3. This will make "healthy skin more attractive." *Id.* at 2.

34. DE590 does not disclose penetration of adenosine to the dermal cells, in the recited concentrations disclosed in the asserted patents or in any amount. On the contrary, DE590 teaches away from such penetration by disclosing that adenosine should be used on the "surface" of the skin in a composition that is applied to the epidermis, which is the visible part of the skin

[1] LOUSA0103359 at 103360.

that may be made "more attractive" by practicing the invention disclosed in DE950. DE590 does not teach proliferation, or the lack thereof, from the use of adenyl derivatives or adenosine.

C. The '213 Patent and CA665

35. The '213 Patent (U.S. Patent No. 3,978,213) and CA665 (its Canadian counterpart, Canadian Patent No. 1023665) disclose using "cyclic AMP" in "topical compositions" to "temporarily soothe and soften skin." '213 Patent at 1:47-50.[2] The "area to be treated" is the skin that the composition is applied to "once, twice or three times daily." *Id.* at 2:22-24. Women using an exemplary formulation disclosed by the '213 Patent "had a more youthful appearance." '213 Patent at 4:1-3.

36. L'Oréal agrees that the '213 Patent "does not relate to adenosine."[3] Moreover, the '213 Patent and CA665 do not disclose penetration of adenosine to the dermal cells, in the recited concentrations disclosed in the asserted patents or in any amount. On the contrary, the '213 Patent and CA665 teach away from such penetration by disclosing that adenosine should be applied in a topical composition to the epidermis, which is the "area to be treated." The visible epidermis may have "a more youthful appearance" when practicing the invention of the '213 Patent and CA665; they are not directed to the dermis. The '213 Patent and CA665 do not teach proliferation, or the lack thereof, from the use of cyclic AMP or adenosine.

D. Franz

37. As discussed in my opening report, Dr. Thomas J. Franz pioneered the "gold standard" diffusion test to model and measure dermal absorption *in vitro.* In the 1983 article cited by Dr. Kasting in his report ("Kinetics of Cutaneous Drug Penetration," published in the November

[2] CA665 makes comparable disclosures; accordingly I reference only the '213 Patent herein.
[3] ADENOSINE_00005498 at 5673.

'164 Patent is directed to the epidermis and teaches away from penetration to the dermis insofar as it discloses that its composition is designed to penetrate past only the stratum corneum and stimulate epidermal growth with its inclusion of "epidermal growth factor." The '164 Patent teaches epidermal proliferation; it does not teach or even suggest the absence of dermal cell proliferation.

H. Schrader

45. Schrader ("Optimizing of Cosmetic Products and Their Effects on Human Skin") discusses the "development pathway of a cosmetic care product," including adenosine triphosphate (ATP) as an ingredient. Schrader at 1, 4. Schrader discloses that "efficacy tests" should be conducted, for example, "[f]or measuring skin hydration," a "corneometer" used to "reflect[ ] the degree of hydration on the skin surface, e.g. the difference before and after treatments of the skin with cosmetic or pharmaceutical products." *Id.* at 9. "[R]oughness testing by quantitative image analysis" is similarly determined with "silicone impression[s]" of the skin's surface. *Id.* at 9-10. This will give the formulator information about the "results of ATP on skin smoothness and skin hydration." *Id.* at 10.

46. Schrader does not disclose using adenosine at all, but instead ATP. Schrader does not disclose penetration of adenosine or ATP to the dermal cells, in the recited concentrations disclosed in the asserted patents or in any amount. On the contrary, Schrader teaches away from such penetration by disclosing that that the disclosed "results of ATP" are directed to "the skin surface." Schrader does not teach proliferation, or the lack thereof, from the use of ATP or adenosine.

I. Rattan

47. Rattan ("Kinetin Delays the Onset of Ageing Characteristics in Human Fibroblasts," published in *Biochemical & Biophysical Research Communications*) discloses that kinetin, a cytokinin (a type of plant hormone), may be used on skin fibroblast cultures *in vitro* to "delay[ ] the onset of many age-related characteristics" without "disturbing their Hayflick limit of cell proliferation." Rattan at 2.

48. Rattan does not disclose using adenosine at all, but rather kinetin. Dr. Kasting refers to kinetin as an "adenosine analog" without citing to any relevant literature supporting the proposition that a skilled artisan would have found it obvious that adenosine should be substituted for kinetin. Nor have I found any such support in my own research. On the contrary, while cytokinins have some structural similarity to adenine (which forms adenosine), structurally similar compounds often have distinct chemical and biological properties.[7] Indeed, in Rattan's own research, he specifically contrasts kinetin with adenosine analogs and cautions skilled artisans not to use adenosine analogs.[8]

J. The '061 Patent

49. The '061 Patent (U.S. Patent No. 5,276,061) discloses "compositions containing 1α-hydroxyvitamin D homolog compounds" for "the treatment of various skin conditions." '061 Patent at 1:11-13; 1:58. In "one embodiment of th[e] invention the composition also contains . . . adenosine or a nucleic acid hydrolysate in an amount of 0.1-1% . . . by weight based on the weight of the composition." *Id.* at 6:5-13. "Topical application . . . of the invention was found to be cosmetically effective" in studies involving field mice, in which the mice were

[7] *See, e.g.*, Chhabra, N., Aseri, M. & Padmanabhan, D. (2013). "A review of drug isomerism and its significance." *Int J. Appl. Basic Med. Res.* 3(1):16-18.
[8] *See infra* ¶¶ 51-52.

"ranked into four groups according to visible wrinkling and overall skin surface roughness," using "[d]etails of the skin surface rich as stratum corneum desquamation, scaling, size and plumpness of skin divisions, [which] were visible on higher magnification." *Id.* at 6:37-39, 7:18-21, 7:29-21. These "visible changes in skin surface condition" supported the invention. *Id.* at 9:21.

50. The '061 Patent does not disclose penetration of adenosine to the dermal cells, in the recited concentrations disclosed in the asserted patents or in any amount. On the contrary, the '061 Patent teaches away from such penetration by disclosing that adenosine should be used in a composition that is applied topically to the epidermis, which is the "visible" part of the "skin surface" that may be improved by practicing the disclosed invention. The '061 Patent does not teach proliferation, or the lack thereof, from the use of adenosine.

K. The '089 Patent

51. The '089 Patent (U.S. Patent No. 5,371,089) discloses "methods and compositions for countering the adverse effects of aging mammalian cells" by applying "compositions containing 6-(substituted amino)purine cytokinins," i.e., "kinetin" to skin fibroblasts. '089 Patent at 1:22-30, 6:57. The '089 Patent contrasts its recommended use of kinetin with the use of "adenosine analogs" on "fibroblast cells," which is not recommended as, when "fibroblast cells are contacted with adenosine analogs," they "exhibit decreased growth rate and a change in morphology from the normal flattened elongated morphology typical of cultured fibroblasts to a very elongated spindle-shape characteristic of cytotoxic response." *Id.* at 7:34-44. "Cytotoxic response" is also referred to as "cell death." According to the '089 Patent, the "very elongated shape of immortalized cells exhibiting this response is not shape characteristic of young, healthy, primary cultures of normal diploid fibroblasts." *Id.* at 7:44-47.

52. The ’089 Patent does not disclose the use of adenosine at all, but instead kinetin. Dr. Kasting refers to kinetin as an “adenosine analog” in his report, but the ’089 Patent specifically contrasts the use of kinetin on fibroblast cells with the use of “adenosine analogs,” and warns against adenosine analogs as likely to lead to cell death. Thus, a skilled artisan familiar with the ’089 Patent would be led directly away from using adenosine, or its analogs, applied to the dermal cells. The ’089 Patent does not teach cell proliferation, or the lack thereof, from the use of adenosine.

L. Singh

53. Singh (“Selective Drug Delivery Through and Within Skin Using Liposomes,” published in the *Indian Journal of Pharmaceutical Science*) discloses that liposomes “seem to have the best potential” to “enhance penetration of active ingredients into the skin.” Singh at 9. Lipsomes “encapsulat[ ]” the active ingredient and are therefore “ideally suited for drug delivery.” *Id.* at 10. “With appropriate formulation, the drug could be targeted even within the skin.” *Id.* at 11. Indeed, liposomes are “able to carry the drug to vascularized dermis.” *Id.* at 15.

M. New Raw Materials Encyclopedia

54. New Raw Materials Encyclopedia (published in *Cosmetics & Toiletries*) lists a product “Unilactamin L-17” from Induchem that contains butylene glycol, hydrolyzed milk protein, niacinamide, and adenosine triphosphate (ATP), which “prevent premature skin aging, [and have] good moisturizing and wrinkle-smoothing properties.” New Raw Materials Encyclopedia at 99-100.

55. New Raw Materials Encyclopedia discloses ATP, not adenosine. It does not teach that ATP has “good moisturizing and wrinkle-smoothing properties.” On the contrary,

57. The ’694 Patent does not disclose using adenosine at all, but rather adenosine phosphate; adenosine is a nucleoside and adenosine phosphate is a nucleotide. The ’694 Patent does not disclose penetration of adenosine or adenosine phosphate to the dermal cells, in the recited concentrations disclosed in the asserted patents or in any amount. On the contrary, the ’694 Patent teaches away from such penetration. It discloses the benefit of moisturizing both “at the surface and in the deeper epidermal and dermal layers,” but teaches that adenosine phosphate is “difficult to dissolve” and will therefore stay on the skin’s surface, whereas “ascorbic acid or vitamin C” will “stimulate collagen” in the dermis. The ’694 Patent does not teach proliferation, or the lack thereof, from the use of adenosine or adenosine phosphate.

O. DE773

58. DE773 (German Patent Application 195 29 773 A1) discloses using “topical or dermatological preparations” for “the regeneration, support, promotion or strengthening of the natural protective and barrier functions of healthy and diseased skin.” DE773 at 2. DE773 is targeted toward the “horny layer of the skin”—i.e., the stratum corneum, the top, surface layer of the epidermis—where the “barrier” function of the stratum corneum is damaged over time, hindering its ability to “protect[ ] the skin. *Id.* DE773 discloses using “topical preparations” to “improve the state of the barrier.” *Id.* at 3. Such topical preparations may include “adenosine” in the amount of “0.001-20% by weight.”

59. DE773 does not disclose penetration of adenosine to the dermal cells, in the recited concentrations disclosed in the asserted patents or in any amount. On the contrary, the DE773 teaches away from such penetration. It is specifically directed toward improving the barrier function of the stratum corneum, which is in the epidermis, not the dermis, and discloses an amount

of adenosine to be applied to the surface of the skin. DE773 does not teach proliferation, or the lack thereof, from the use of adenosine.

P. DE107

60. DE107 (German Patent Application 195 45 107 A1) is titled "[u]se of adenosine for enhancing cell proliferation in human skin" and discloses "the use of adenosine in cosmetic and dermatological preparations." DE107 at 1. DE107 teaches that aging skin results in "a number of degenerative process whose results include . . . structural changes an insult in the dermis and epidermis." *Id.* Those changes include "[i]nvolution of the microvascular system," "[l]oosening and formation of wrinkles in part due to the reduction and cross-linking of collagen and accumulation of glucosaminoglycans," "[f]lattening of the reticular plug," the "surface reduction between dermis and epidermis," "limited regenerative turnover in the epidermis in conjunction with abnormal formation of the horny layer (hornification) that leads to drying out of the skin," "[a]bnormal regulation of cell division (proliferation) and cell maturation (differentiation) in the epidermis resulting in atypical cells and polarity loss," and "[l]ocal hyper-, hypo-, and abnormal pigmentations (age spots)." *Id.* DE107 teaches that it addresses aging skin with "enhancement of cell proliferation." *Id.* at 2. Dr. Kasting apparently agrees that DE107's discussion of cell proliferation is limited to epidermal cell proliferation. The only adenosine measurement provided by DE107 discloses the amount of adenosine in the topically applied composition, which is "is preferably 0.001% by weight to 10% by weight, and particularly 0.01% by weight to 6% by weight relative to the total weight of the preparations." *Id.* at 14. As discussed in more detail below, DE107 discloses exemplary formulations, which omit a number of ingredients as well as manufacturing instructions, leaving those elements to the discretion of the formulator.[10]

[10] *See infra* ¶¶ 91-101.

R. JP915

66. JP915 (Japanese Patent Application H9-295915) was published on November 18, 1997, and, as discussed further below, is not prior art.[18] JP915 discloses the use of adenosine 3',5'-cyclic phosphate to "prevent[ ] and improve[ ] rough skin and small wrinkles due to aging of skin." JP915 at 2. JP915 explains that "a cosmetic using a derivative of acyl cAMP wherein the N^6 and 2'-O positions of the adenosine 3', 5'-cyclic phosphate (referred to as cAMP hereinafter) are acyl groups," but "this has drawbacks such as the results not being sufficient, the acyl form being unstable, and an unpleasant odor due to decomposition occurring, and thus practicality is limited." *Id.* at 2-3. JP915 teaches that "a specific cAMP derivative has excellent collagen production promotion action and activates skin cells." *Id.* at 3.

67. JP915 does not disclose the use of adenosine. Dr. Kasting refers to the disclosed "specific cAMP derivative" as "adenosine-related compounds," without citing to any literature supporting the proposition that a skilled artisan would have found it obvious that adenosine should be substituted for the disclosed specific cAMP derivative. On the contrary, JP915 teaches away from using any compound other than the "specific cAMP derivative" disclosed, explaining that they have substantial "drawbacks" and directing skilled artisans to use only the disclosed "specific" compounds.

S. JP541

68. JP541 (Japanese Patent Application H10-7541) was published on January 13, 1998, and, as discussed further below, is not prior art. [19] JP541 discloses "an external preparation for skin" created by "containing one or two or more of types of lipoic acid, salts, and derivatives

[18] *See infra* ¶¶ 78-85.
[19] *See infra* ¶¶ 78-85.

thereof, and one or two or more types selected from among a group made up of vitamin A and derivatives thereof; carotenoids; riboflavin and derivatives thereof; vitamin E and derivatives thereof; vitamin K; adenosine and derivatives thereof; and flavonoids and tannin." JP541 at 1. The "compound amount" for each of these potential ingredients will be "around 0.01 to 10.0% by weight, respectively." *Id.* at 5. The disclosed composition will be "effective" in "improving and preventing action and whitening action of rough skin or symptoms of aging skin," *id.* at 3-4, as well as addressing "stains on the skin that occur along with sunburns by ultraviolet radiation or aging," *id.* at 5.

69. The JP541 does not disclose penetration of adenosine to the dermal cells, in the recited concentrations disclosed in the asserted patents or in any amount. On the contrary, JP541 teaches away from such penetration, explaining its benefits exist at the surface of the skin, such as improvements in "whitening action" and "stains on the skin." JP541 does not teach proliferation, or the lack thereof, from the use of adenosine.

T. The '428 Patent

70. The '428 Patent (U.S. Patent No. 5,763,428) issued on June 9, 1998, and, as discussed further below, Dr. Kasting has not established it is prior art. [20] The '428 Patent discloses "a pharmaceutical composition which includes a pharmaceutically effective amount of the novel 1α-hydroxy vitamin D4 compounds," and "a method of controlling abnormal calcium metabolism by administering a pharmaceutically effective amount of the novel compound." '428 Patent at 1:19-24. The '428 Patent discloses that its invention is appropriate for a broad array of uses, including "the treatment of abnormal metabolism of calcium and phosphorus," *id.* at 4:12-14, treating "liver failure, renal failure, gastrointestinal failure," *id.* at 4:16-18, treating

[20] *See infra* ¶¶ 78-85.

"prophylactically or therapeutically vitamin D deficiency diseases and related diseases, for example, renal osteodystrophy, steatorrhea, anticonvulsant osteomalacia, hypophosphatemic vitamin D-resistant rickets, osteoporosis, including postmenopausal osteoporosis, senile osteoporosis, steroid-induced osteoporosis, and other disease states characteristic of loss of bone mass, pseudodeficiency (vitamin D-dependent) rickets, nutritional and malabsorptive rickets, osteomalacia and osteopenias secondary to hypoparathyroidism, post-surgical hypoparathyroidism, idiopathic hypoparathyroidism, pseudohypoparathyroidism, and alcoholism, *id.* at 4:19-30, "hyperproliferative skin disorders such as psoriasis, eczema, lack of adequate skin firmness, dermal hydration and sebum secretion," *id.* at 4:33-35, "inhibiting the hyperproliferative activity of malignant cells, i.e., cancer cells," *id.* at 4:50-51, "the treatment of breast cancer and colon cancer," *id.* at 5:4, and "the treatment of noncancerous skin disorders such as dermatitis, contact and ectopic," *id.* at 5:15-16. While the '428 Patent discloses 2 out of 25 embodiments that contain adenosine, *see* Examples 13 and 17, it does not disclose which of the many disclosed ailments and/or conditions those examples are meant to treat.

71. The '428 Patent does not disclose penetration of adenosine to the dermal cells, in the recited concentrations disclosed in the asserted patents or in any amount. On the contrary, the '428 Patent teaches away from such penetration, disclosing only that adenosine may be used in topical compositions which, as far as a skilled artisan would deduce, are for treating epidermal conditions such as psoriasis. The '428 Patent does not teach proliferation, or the lack thereof, from the use of adenosine.

U. Barker

72. Barker ("Cosmetic Industry: Newer Cosmetic Ingredients—New Patch Testing Problems?" in *American Journal of Contact Dermatitis*) was published in June 1998 and, as

discussed further below, is not prior art. [21] Barker discusses "new cosmetic ingredients," including "Cyclic AMP" and "Kinetin." Barker at 132.

73. Barker does not disclose using adenosine at all, but rather cyclic AMP and kinetin. L'Oréal agrees that cyclic AMP "does not relate to adenosine."[22] Similarly, as discussed above, Dr. Kasting refers to kinetin (and cyclic AMP) as "adenosine analogs" without citing to any relevant literature supporting the proposition that a skilled artisan would have found the purported interchangeability of these ingredients obvious, which is not supported by my own research, and is contradicted by L'Oréal's own cited prior art.[23] Barker does not disclose penetration of adenosine to the dermal cells, in the recited concentrations disclosed in the asserted patents or in any amount. According to Barker, cyclic AMP "promote[s] more energetic cellular metabolism," but Barker does not disclose that "cellular metabolism" is thought to occur in the dermal cells, and I have seen no evidence to support that.

V. WO206

74. WO206 (International Patent Publication WO 98/46206) was published on October 22, 1998, and, as discussed below, is not prior art. [24] WO206 discloses that "[i]t has been unexpectedly discovered that a skin cream composition containing alpha-alanine, a ribose compound, ascorbic acid, nicotinic acid, and a water-based cream is safe and effective in treating skin damage caused by non-cancerous conditions." WO206 at 1. WO206 explains that the object of its invention is to "treat[ ] acne," "reduce skin inflammation and inflammatory conditions such as eczema, psoriasis, and both endogenous and contact dermatitis." *Id.* at 2. According to WO206,

[21] *See infra* ¶¶ 78-85.
[22] ADENOSINE_00005498 at 5673.
[23] *See supra* ¶ 52.
[24] *See infra* ¶¶ 78-85.

in addition to the primary ingredients, the composition may "also contain an adenosine compound, i.e. adenosine or an adenosine derivative that is advantageous to the metabolic activity of cells," in an amount of "at least 0.01 wt %, preferably at least 0.02 wt %, and more preferably at least 0.04 wt %, based on the total weight of the composition." *Id.* at 5-6.

75. WO206 does not disclose penetration of adenosine to the dermal cells, in the recited concentrations disclosed in the asserted patents or in any amount. On the contrary, WO206 teaches away from such penetration, disclosing only that adenosine may be used in topical compositions which, as far as a skilled artisan would deduce, are for treating epidermal conditions such as acne and psoriasis. WO206 does not teach proliferation, or the lack thereof, from the use of adenosine.

W. The '062 and '272 Patents

76. The '062 Patent (U.S. Patent No. 5,889,062) and the '272 Patent (U.S. Patent No. 5,912,272) issued on March 30, 1999 and June 15, 1999, respectively, and, as discussed further below, Dr. Kasting has not established they are prior art. [25] The '062 Patent and '272 Patent disclose the use of "ubiquinones and plastoguinones" in "cosmetic or dermatological formulations." '062 Patent at 1:65-2:12.[26] The invention may be used to address "aging-related structural damage and disfunctions" such as "[d]ryness, roughness and the development of dryness wrinkles," "itching," "reduced re-oiling by sebaceous glands (even after washing)," "visible dilation of vessels (couperosis)," "flaccidity and development of folds," "local hyper- and hypopigmentation and defective pigmentation (for example senile keratosis)," and "increased susceptibility to mechanical stress (for example cracking)." *Id.* at 1:8-31. These conditions occur

[25] *See infra* ¶¶ 78-85.
[26] The '272 Patent makes comparable disclosures; accordingly I reference only the '062 Patent herein.

in the "epidermis and dermis," *id.*, but the only identified dermal structures are the sebaceous glands and vessels. The invention can also include "0.01-10 per cent by weight" of "substances or substance combinations of aerobic cell energy metabolism, for example cell energy transfer agents (such as kreatin, guanine, guanosine, adenine, adenosine, nicotine, nicotinamide or riboflavin)." *Id.* at 4:25-30.

77. The '062 and '272 Patents do not disclose penetration of adenosine to the dermal cells, in the recited concentrations disclosed in the asserted patents or in any amount. On the contrary, the '062 and '272 Patents teach away from such penetration by disclosing that adenosine is directed to "cell energy metabolism," but identifying only non-cellular structures located in the dermis. Thus, a skilled artisan following the '062 and '272 Patents would be led toward using adenosine at the surface of the skin to treat, for example, keratosis, which stems from keratinocytes, the primary cell type in the epidermis. The '062 and '272 Patents do not teach proliferation, or the lack thereof, from the use of adenosine.

III. PRIORITY DATE

78. I have been informed and understand that the parent application to the asserted patents was filed on October 26, 1998. I also have been informed and understand that the "critical date" for the asserted patents with respect to identifying certain types of prior art is one year prior to the date of the parent application, October 26, 1997. I also understand and have been informed that subject matter that was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, after the invention described in the asserted patents and after the "critical date," is not prior art.

79. I understand and have been informed that in approximately 1996, Drs. Dobson and Ethier decided to investigate the effect of applying adenosine to human dermal fibroblasts and

CERTIFICATION OF COMPLIANCE

The foregoing document complies with the type-volume limitation of this Court's March 2, 2020 form Scheduling Order For All Cases where Infringement is Alleged. The text of this brief, including footnotes, was prepared in Times New Roman, 14 point. According to the word processing system used to prepare it, the brief contains 679 words, excluding the case caption, signature block, table of contents and table of authorities.

/s/ Brian E. Farnan
Brian E. Farnan (Bar No. 4089)

Dated: October 16, 2020